

REMARKS

I. Detailed Action

Applicant respectfully reiterates that the election of claims 1-19 was made **with traverse** as indicated in the Response to Restriction Requirement on October 10, 2002. The Applicant further submits that claims 20-22 are canceled as being drawn to nonelected claims in accordance with 37 C.F.R. § 1.144, as requested by the Examiner.

Applicant acknowledges that the declaration by William E. Marshall filed under 37 C.F.R. § 1.132 was fully considered by the Examiner in the office action of May 30, 2003. However, the Examiner states the Figures were unreadable and thus given no consideration. Applicant respectfully offers the Figures have been re-submitted with the Substitute Amendment After Final filed on May 30, 2003 and are being submitted in this Preliminary Amendment and requests consideration.

II. Claim Rejections – 35 U.S.C. § 112, Second Paragraph

Claims 17-19 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Examiner states claims 17-19 are vague and indefinite for the phrase "sequential periods of stress" as it is unclear what is meant by the phrase.

Applicant respectfully traverses this rejection. However, in an effort to expedite prosecution Applicant has amended claim 17 to include the terminology --at least two or more sequential periods of stress wherein each period of stress is approximately 10-20 minutes--, thereby further defining the phrase "sequential periods of stress" as supported by the specification, thus alleviating this rejection (see page 12). Therefore, Applicant asserts that claims 17-19 as amended are not indefinite and would be understood by one skilled in the art. Applicant requests reconsideration.

Claim 12 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Examiner states claim 12 is vague and indefinite by the phrase "stress response factors (SRFs)<10kDa" as it is unclear what is meant by said term.

Applicant has amended claim 12 to delete the terminology "<10kDa" and included the language --with a molecular weight less than 10kDa--, as suggested by the Examiner, thereby alleviating this rejection.

In light of the above amendment and remarks, Applicant asserts the claims are now in a condition for allowance. Applicant respectfully requests reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, second paragraph.

III. Claim Rejections – 35 U.S.C. § 103(a)

Claim Rejections - 35 U.S.C. 103 over De Vuyst et al.:

Claims 1-8 and 10-19 remain rejected under 35 U.S.C. § 103(a) as obvious over De Vuyst et al. as the Examiner states that De Vuyst suggests that low molecular weight proteins (bacteriocins) are produced by stressed bacteria.

Applicant respectfully traverses this rejection. Applicant asserts that the cited reference does not teach, nor does it suggest, the claimed unique invention of the present application.

Applicant would like to reiterate that in contrast to the bacteriocins described in De Vuyst et al., the present invention claims the activation and modulation of the immune system of an animal through the administration of compositions harvested from stressed bacteria which include stress response factors (SRFs) that activate and modulate circulating macrophages. The SRFs stimulate the immune system and it is the host immune system that battles invading bacteria, not other bacteria or bacteriocins. De Vuyst et al. does not disclose the production of SRFs in bacteria and the administration of the SRFs to an animal which has been filtered to remove any molecules larger than 10kDa from the bacteria as taught in the present invention. Further, the bacteriocins of De Vuyst et al. are peptide metabolites filtered to obtain a filtrate containing particles of greater than 10kD and therefore cannot by definition be present in Applicant's materials. De Vuyst et al. teaches nothing about small factors different from bacteriocins that can stimulate the immune system upon administration. The SRF composition of the present invention does not include bacteriocins (peptides) or other compositions with bactericidal properties as disclosed in the § 132 Declaration of March 17, 2003.

Submitted herewith for the Examiner's consideration is a § 132 Declaration of the inventor that clearly teaches how Applicant's invention is not related to bacteriocins. The

attached § 132 Declaration describes methods and results used to identify the nature of the intracellular solutes which form the basis of Applicant's invention. The intracellular solutes are a mixture of 10-13 oligoribonucleotides, containing from 1 to 5 nucleotides plus the base uracil, formed by the destruction of ribosomes. Attached to the § 132 Declaration are copies of pages from the Applicant's lab notebook that display figures of the separation of the intracellular solutes on HPLC (high pressure liquid chromatography) that indicate 13 different peaks or components present in Applicant's composition. Also attached to the Declaration are copies of pages that display figures of the separation of the intracellular solutes on a Sephadex column, which indicate the presence of 1-5 families of nucleotides. In addition, copies of pages from the Applicant's lab notebook that displays analyses of the intracellular solutes on TLC (thin layer chromatography) which demonstrate the presence of oligoribonucleotides and uracil are attached. The § 132 Declaration clearly shows there is no evidence of the presence of proteins or peptides among the intracellular solutes. In contrast, De Vuyst only teaches bacteriocins which are bioactive peptides (see De Vuyst et al., page 817). Applicant respectfully requests that the present § 132 Declaration be entered and made of record.

Earlier Declarations in the present application's prosecution show that the released intracellular solutes lacked any bacteriocin-like activity thus exemplifying how the cited reference does not teach or suggest the claimed invention as a whole and thus would not have been obvious to one of skill in the art according to MPEP § 2141.02. Applicant finally asserts that the instant claims are not drawn to "all" factors produced in response to nutrient deprivation but rather to stress response factors only with a molecular weight of less than 10kDa, which are oligoribonucleotides as disclosed in the § 132 Declaration, and that are exposed to stress and promote activation and modulation of the immune system. In contrast, De Vuyst et al. only suggests peptides (bacteriocins) that are larger than 10kDa may be manipulated to stimulate bacteriocin production under unfavorable growth conditions.

Further, Applicant is resubmitting the Figures from the § 132 Declaration of March 17, 2003. The following is solely to reiterate what these figures illustrate in regards to the present invention and the cited reference of De Vuyst et al. These figures, in conjunction with the considered § 132 Declaration of March 17, 2003, clearly establish that the SRF compositions of the present invention do not include bacteriocins or other compositions with bactericidal

properties. The declaration detailed several experiments conducted using the standard methods in the art and even used by De Vuyst exposing the test strain for bacteriocins, *Lactobacillus helveticus*, ATCC 15009, to the SRF compositions. The results show that the SRF compositions do not exhibit bactericidal activity. The results as depicted in **Figure 1** demonstrate that the preparations of the invention obtained from *L. monocytogenes*, *L. plantarum*, and *E. faecium* do not inhibit growth of *Lactobacillus helveticus*. This is in stark contrast to the bacteriocin Nisin which is shown at the asterisk. **Figure 2** shows that stressing *L. monocytogenes*, or even twice stressing *L. plantarum* and *E. faecium* or stressing heat killed *L. plantarum* and *E. faecium* do not result in bacteriocidal activity against *L. helveticus*. Finally in **Figure 3**, 7 test strains (5 of *L. plantarum* and 2 of *E. faecium*) were used both as SRF collecting strains and as test strains. Again, the bacteriocin Nisin inhibited all 7 strains while the SRFs collected from the same strains as well as from *L. caseii* did not inhibit growth. Therefore, Applicant respectfully requests that this ground of rejection be withdrawn.

Claim Rejections - 35 U.S.C. 103(a) over De Vuyst et al. in view of Nanji:

Claims 1-8, 10-15, and 17-19 remain rejected under 35 U.S.C. § 103(a) as obvious over De Vuyst et al. in view of Nanji as the Examiner states the cited references disclose that administering lactic acid bacteria to animals for protection against endotoxin-mediated shock.

Applicant respectfully traverses this rejection. Applicant reiterates as disclosed *supra* that the bacteriocins disclosed in De Vuyst et al. are not taught or suggested in the present invention that specifically teaches SRFs of a molecular weight of less than 10kDa. In addition, Nanji does not teach or suggest in combination with De Vuyst et al. any SRFs factors at a molecular weight of less than 10kDa that modulate the immune responses of animals as disclosed in the present invention. Nanji only claims *Lactobacillus GG* with a biocompatible carrier to form a preparation that results in a reduction in the quantity of endotoxin within a mammal's blood plasma. The claimed lactobacillus in Nanji is a single strain and is not present in all stressed bacteria as in the present invention.

Further, Applicant asserts that only bacteria grown into their late exponential phase, or into their stationary phase or into dormancy contain Applicant's claimed intracellular solutes consisting of immune-stimulating oligoribonucleotides as in the present invention. Nanji does

not teach or suggest this significant feature. In contrast, Nanji only teaches a lactobacillus that is acid resistant and able to destroy Gram-negative bacteria in the gastrointestinal tract. Applicant also asserts that the instant claims are not drawn to "any" or "all" factors produced in response to nutrient deprivation but rather to stress response factors having a molecular weight of less than 10kDa only, which are oligoribonucleotides as disclosed in the § 132 Declaration submitted herewith, that are exposed to stress and promote activation and modulation of the immune system. Thus neither of the cited references alone or in combination teach, suggest or even mention stress response factors described in Applicant's specification which are distinct and non-obvious. It is required that "both the suggestion and the expectation of success must be found in the prior art, not in the applicant's disclosure" and this is not accomplished in regards to De Vuyst et al. in view of Nanji. *See In re Dow Chemical Co.*, 837 F.2d 469 (Fed. Cir. 1988). One ordinarily skilled in the art would not be motivated to combine the cited references to produce and administer Applicant's SRFs with a molecular weight of less than 10kDa to activate and modulate the immune system of an animal.

Claim Rejections - 35 U.S.C. 103(a) over De Vuyst et al. in view of Perdigon:

Claim 16 remains rejected under 35 U.S.C. § 103(a) as obvious over De Vuyst et al. in view of Perdigon as the Examiner states the Perdigon discloses the use of low molecular weight proteins as adjuvants.

Applicant traverses this rejection. Applicant reiterates as disclosed *supra* that the bacteriocins disclosed in De Vuyst et al. are not taught or suggested in the present invention that specifically teaches SRFs of a molecular weight of less than 10kDa. Applicant asserts there is no suggestion in Perdigon, which is distinct and different from the claimed invention, that is directed to the present invention's SRFs of low molecular weight of less than 10kDa, that are oligoribonucleotides, not proteins or peptides, as disclosed in the § 132 Declaration. Further, Perdigon does not suggest the administration of the claimed invention's SRFs to modulate the animal's immune response. In contrast, Perdigon teaches that the health benefits of feeding milk fermented with lactobacilli is due to an interaction between the bacteria and the milk solids. Perdigon teaches that these effects were limited to and based upon the presence of milk and teach away from the use of stressed bacteria alone as in the present invention. Therefore, Applicant

asserts De Vuyst et al. in combination with Perdigon do not render obvious the Applicant's invention as defined by the claims.

In light of the above remarks and the amended claims, Applicant asserts that the combination of references cited by the Examiner do not teach or suggest the unique method of the present invention and thus would not be obvious to one of ordinary skill in the art. Applicant submits that none of the cited references teach or suggest the inventive method and composition described and claimed in the present invention. When looking at a combination of prior art references, two factors must be considered: (1) whether the prior art would have suggested to one of ordinary skill in the art that they should make the claimed invention; and (2) whether the prior art would also have suggested a reasonable expectation of success to those of ordinary skill. In re Vaeck, 947 F.2d 488 (Fed. Cir. 1991). However, "both the suggestion and the expectation of success must be found in the prior art, not in the applicant's disclosure... In determining whether such a suggestion can be fairly gleaned from the prior art, the full field of the invention must be considered for the person of ordinary skill is charged with knowledge of the entire body of technical literature, including that which might lead away from the claimed invention." In re Dow Chemical Co., 837 F.2d 469 (Fed. Cir. 1988). Applicants strongly assert that neither the suggestion of the claimed unique invention of the present application nor any expectation of success is taught in the references cited by the Examiner. In fact, Applicant respectfully submits that any such suggestion would be merely hindsight application of the Applicant's specification and claimed invention to the cited references. Applicant respectfully requests reconsideration and withdrawal of the rejection to claims 1-8 and 10-19 under 35 U.S.C. § 103(a).

IV. Conclusion

In light of the above amendments and remarks, Applicants assert that the claims as amended are in condition for allowance. Applicants respectfully request reconsideration and withdrawal of the above rejections to claims 1-8 and 10-19. If it is felt that it would aid in prosecution, the Examiner is invited to contact the undersigned at the number indicated to discuss any outstanding issues.

No other fees or extensions of time are believed to be due in connection with this amendment; however, consider this a request for any fees inadvertently omitted, and charge any additional fees to Deposit Account No. 26-0084.

Reconsideration and allowance is respectfully requested.

Respectfully submitted,



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